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RE: PERCHLORATE CHARGE QUESTIONS

In response to the Federal Register Notice [81 FR 67350 (September 30, 2016)] and on behalf of the Perchlorate Study Group (PSG),[1] Intertox is pleased to submit comments regarding the charge questions.

Given that this is the first time EPA will develop a Maximum Contaminant Level Goal (MCLG) using Biologically Based Dose Response (BBDR) modeling and that the BBDR is complex, novel and potentially controversial, and will be influential, the PSG is committed to assisting EPA in its goal to use the best available science. The PSG has worked with EPA for more than 15 years to provide scientific information to derive and adhere to the basic standards of quality, objectivity, utility and integrity. It is with this spirit, Intertox provides comments on the peer review.

According to EPA's Peer Review Handbook (2015), there are two types of questions for an effective peer review. The first identifies technical and scientific issues on which the Agency would like feedback. The second invites broad evaluation of the overall work product.[2]

The EPA's charge questions are found here. Seven questions are included in the Draft Charge Questions.

Broad Evaluation Type Questions / Comments

None of EPA's seven listed charge questions addresses a broad evaluation of the BBDR work product and instead all questions listed are technical. The noticeable absence of these broader questions represents a substantial gap in the rigor of the peer review. The Draft Charge Questions would benefit greatly by the evaluation of this specific model for the purpose it is used.

One of the overarching concerns about a proper evaluation of a complex model is the magnitude of material a peer reviewer must go through, particularly given that most of the interim peer reviewers have no demonstrated PBPK/BBDR modeling experience. For example, there are two distinct models, each of which has thousands of lines of code and more than 500 variables. The model code was provided for use on two software platforms; however, one of these is no longer available, a scenario which further limits rigorous review of the model.

The peer reviewers should be asked to comment on the duration of time allowed for review as well as the adequacy of resources provided to review the literature database for perchlorate. We are concerned that EPA did not provide adequate time to conduct a comprehensive review of this model.

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[1] *The Perchlorate Information Bureau is supported by Aerojet Rocketdyne, American Pacific Corporation, Lockheed Martin and Orbital-ATK. These companies have worked cooperatively with the U.S. Environmental Protection Agency to increase scientific and medical understanding of perchlorate's risk to human health.*

[2] https://www.epa.gov/sites/production/files/2015-10/documents/epa_peer_review_handbook_4th_edition_october_2015.pdf

It would be beneficial for peer reviewers to be given access to, and encouraged to read, the Agency's *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency*.[3] It would help the peer reviewers to understand how important data quality is to the Agency and provide guidance on addressing the charge questions it raises.

When a charge question asks, for example, "Does the developed model structure adequately and accurately describe the physiology…," what is meant by the term "adequately"? It would help the peer reviewers to understand the level to which they need to evaluate the model. There are many examples of these ambiguous phrases throughout the charge questions. Such undefined terms make it difficult for any peer reviewer to provide a consistent and thorough standard of assessment.

It is unclear why EPA is focused on the pregnant woman and fetus, lactating woman, and infant in exclusion of other life stages. Giving scientific rationale for this policy decision will be useful to the peer review panel as well as the general public. We note that using the results of the Agency's model to support this conclusion is insufficient evidence, as *the model itself* is at issue. Citing empirical evidence published in peer reviewed studies that directly compare adverse effects in these three life stages is the appropriate support.

Given the robust dataset for perchlorate, the Agency can also include a number of secondary sources of information from authoritative bodies should they need more information to address their questions. Notable examples that should not be overlooked include: National Research Council's 2005[4] evaluation of perchlorate and ATSDR's 2010 Toxicology Profile for perchlorate.[5]

Technical and Scientific Type Questions / Comments

Regarding the technical questions, there are topics EPA could expand on in its charge questions in order to ensure that the BBDR model is able to predict the physiology and pharmacology of perchlorate at low environmental doses. We have provided recommendations below:

- *Hypothyroxinemia as a clinical endpoint.* A clinician would test an individual for TSH and not necessarily test for free T4; additionally, hypothyroxinemia is not necessarily an adverse effect in a pregnant or lactating woman; to the point, the American Thyroid Association recommends *not* treating hypothyroxinemia. In the infant, hypothyroxinemia is also not recognized as an adverse effect that warrants treatment and there are no reference levels for this in infants. Is the model accurate to make predictions on health outcomes if the only output is fT4 (and total T4) rather than other relevant thyroid hormone parameters (i.e., TSH)? Explain the scientific support for only using fT4 and provide strong support for the exclusion of the other thyroid markers. The EPA is not a medical organization and the model developers are not clinicians, yet the output and interpretation of the model is to define disease. Does this model accurately predict disease in either the individual or a hypothetical population?
- *Exposure to other goitrogens.* EPA Office of Inspector General (OIG) has demonstrated that perchlorate accounts for less than 2% of the total dietary goitrogen load on a daily basis. How should the peer reviewers reconcile the fact that this model does not include nitrate and thiocyanate (as a minimum) in the model? How do peer reviewers assess the ability for the model to predict adverse outcomes on thyroid hormones given this limitation? Given the pharmacology and toxicology background of perchlorate and other goitrogens, can the model

[3] https://www.epa.gov/sites/production/files/2015-08/documents/epa-info-quality-guidelines.pdf
[4] https://www.nap.edu/catalog/11202/health-implications-of-perchlorate-ingestion
[5] https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=895&tid=181

be further enhanced scientifically in a way that would improve the prediction capability?

- *Doses evaluated are not environmentally relevant.* There are no studies that demonstrate that perchlorate causes hypothyroxinemia in pregnant women, lactating women, or infants at any dose. Consider the doses in EPA's supporting document:
  - "…lactating mothers were predicted to become hypothyroxinemic or hypothyroid at 23 perchlorate exposures below 20 µg/kg/d, even with daily iodine intakes of 250 µg/d." The dose noted (20 µg/kg/d) would be equivalent to a water concentration of 746 ppb, assuming a body weight of 74.6 kg as EPA did in the BBDR model and a drinking water intake rate of 2 L every day).
  - "…the mother stays within the reference range during both pregnancy and lactation as long as perchlorate 14 exposures are below 4 µg/kg/d." Using the same assumptions, the dose of 4 µg/kg/d is equivalent to a water concentration of 149 ppb.

  The model does not predict a linear dose-response relationship. How do responses at high doses relate to doses EPA is considering for regulation? How does EPA reconcile that the doses in clinical studies are orders of magnitude higher than the doses that the model is being asked to use to predict fT4?
- Model predictions are not consistent with the known mechanism of action (MOA). The MOA for perchlorate has been well-recognized and undisputed for decades; that is, perchlorate reversibly blocks iodide uptake (iodide uptake inhibition; IUI) to the thryroid which, if significant (~75% IUI; NRC, 2005) and sustained for months, could result in a decrease in thyroid hormones (e.g., fT4). IUI is a non adverse effect and a clear precursor to an actual adverse effect; the accepted No Observable Effect Level (NOEL) for IUI is 7 µg/kg-d (Greer et al., 2002). Importantly, no other effects occur unless IUI occurs first. EPA should ask the peer reviewers to consider why its model predicts changes in fT4 at doses lower than those it predicts changes in IUI (via RAIU) and the recognized threshold for IUI in the literature.
- *Biological compensation and homeostasis.* What is the scientific assessment of the degree that the model incorporates homeostatic mechanisms? For example, what would the impact on the model be if it included up-regulation of the Sodium-Iodine Symporter?
- *Prediction of steady state is unrealistic.* Iodine and perchlorate intake fluctuate daily. What is the impact of the model output if the dose of perchlorate is steady-state versus the normal variable consumption of food and water?

Thank you for the opportunity to provide these comments.

Sincerely,

Richard C. Pleus, PhD
Intertox, Inc.